PATENT SPECIFICATION (11) 1 269 484

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NO DRAWINGS

(21) Application No. 29539/70 (22) Filed 18 June 1970

(31) Convention Application No. 836 647 (32) Filed 25 June 1969

(31) Convention Application No. 30294 (32) Filed 20 April 1970 in

(33) United States of America (US)

(45) Complete Specification published 6 April 1972

(51) International Classification C 07 d 51/00, 51/34, 51/38, 51/76 57/00, 99/02; A 61 k 27/00

(52) Index at acceptance

C2C 171—27X—289 172—195—285 17X—186—272 180—199—280 183—193—277 18X—187—284 18X—197—277 1E7B1 1E7C1 1E7D1 1E7E1 1E7H2 1E7L 1E7N5 1Q11D 1Q11G 1Q11J 1Q4 1Q6C 1Q7A 1Q8A 1Q8C 1Q9D1 1Q9D2 1Q9D3 1Q9F1 1Q9F2 214 215 220 225 226 22Y 250 252 255 25Y 305 30Y 311 313 314 31Y 321 323 326 32Y 332 338 342 34Y 351 352 355 364 365 366 367 368 36Y 373 37Y 396 397 3A10E1 3A12A4A 3A12B3 3A12C6 3A19A4 3A19B2 3A19C3 3A19D2 3A7V1A4 3A7V1E2 3A7V1F1 3A7V1F2 3A7V1J1 3A7V1P 3A7V1Q 3A7V2A4 3A7V2E2 3A7V2F1 3A7V2J1 3A7V2K2 3A7V2Q 3A7V3A4 3A7V3E1 3A7V3E2 3A7V3J2 3A7V3J3 3A7V3J4 3A7V3K1 3A7V3K2 3A7V3L 3A7V3P 3A7V4A4 3A7V4E1 3A7V4E2 3A7V4F1 3A7V4J2 3A7V4J3 3A7V4J4 3A7V4K2 3A7V4L 464 490 491 509 50Y 574 584 594 613 620 621 623 624 625 628 62X 631 638 658 65X 660 661 662 670 672 675 676 678 67X 680 681 682 694 697 699 761 762 790 79Y KH KJ KK KP KR KS KT KV LK LS LW LZ MD MM QT RC RE RM

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(54) ARYLPYRAZINE AND ARYLPYRIMIDINE CARBOXYLIC ACIDS AND THEIR DERIVATIVES

(71) We, MERCK & Co. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Despite all the research carried on in the development of anti-inflammatory drugs in the past two decades, our knowledge of inflammation remains largely descriptive and there has been little progress; however, a great many new drugs have appeared. Many of these have been steroids of the 11-oxygenated pregnane series. These, while effective, are complex in structure, and there is a need for equally effective compounds of simpler structure.

This invention is concerned with aryl pyrazine and pyrimidine carboxylic acids and their non-toxic pharmaceutically acceptable salts, esters and amides, processes for preparing these compounds and their use as medicinal agents.

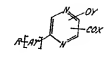
The invention embraces compounds of the following types:

A. 2-aryl-5-hydroxy-4-pyrimidine carboxylic acids
B. 2-aryl-4-hydroxy-5-pyrimidine carboxylic acids
C. 2-aryl-5-hydroxy-6-pyrazine carboxylic acids
D. 2-aryl-6-hydroxy-5-pyrazine carboxylic acids

The compounds of this invention have the general formula:

I

or



II

in which —COX and —OY are ortho to each other; [Ar] is a benzenoid or non-benzenoid aromatic structure attached to the pyrimidinyl or pyrazinyl ring either directly or through a system containing conjugated double bonds and containing one or more R radicals or atoms which may be at any position on the ring; R is a hydrogen or halogen atom or an alkyl, alkenyl, haloalkyl, hydroxy, alkoxy, acyloxy, nitro, amino, alkylamino, dialkylamino, acylamino, mercapto, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfamoyl or aminosulfinyl radical; X is a hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, N-attached N-heterocyclo, alkoxy or aralkoxy radical or a radical of formula OM, where M is an alkali metal or an equivalent of an alkaline-earth metal, magnesium or aluminium; and Y is a hydrogen atom or an alkyl, alkenyl, aralkyl, aryl, acyl or alkoxycarbonyl radical, with the proviso that Y and/or at least one R is other than hydrogen when X is hydroxy. [Ar] may be a heterocyclic radical, though preferably it is phenyl, styryl or naphthyl, and any R substituent is preferably at the 4-position of [Ar].

The alkyl, alkoxy and alkenyl radicals and residues mentioned preferably contain not more than five carbon atoms.

When R is a halogen it is preferably fluorine or chlorine. Other possible values of R include methyl, ethyl, propyl, *i*-propyl, vinyl, allyl, trifluoromethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, methylethylamino, acetamido, benzoylamino, methylthio, ethylthio, methylsulfonyl and methylsulfinyl.

Possible values of X include methylamino, ethylamino, dimethylamino, methylethylamino, N-piperidino, N-morpholino, N-piperazino, N-homopiperazino, N-pyrrolidino, methoxy and ethoxy. When X is OM, specific values of M include sodium, potassium and calcium, as well as magnesium and aluminium.

Possible values of Y include methyl, ethyl, propyl, *i*-propyl, butyl, *s*-butyl, *t*-butyl, allyl, vinyl, methallyl, benzyl, phenethyl, phenyl, acetyl, propionyl, benzoyl, methoxy carbonyl and ethoxy carbonyl.

In preferred compounds of this invention, R—[Ar] is phenyl or halophenyl; X is hydroxy, amino, dimethylamino, methoxy or ethoxy; and Y is hydrogen or acetyl, with the proviso that R—[Ar] must be halophenyl when Y is hydrogen and X is hydroxy. Particularly suitable compounds are those in which R—[Ar] is halophenyl, X is hydroxy and Y is hydrogen.

It has been found that the compounds of this invention have a useful degree of anti-inflammatory activity and are effective for the prevention and inhibition of oedema and granuloma tissue formation and in the treatment of arthritic and dermatological disorders and in like conditions which are responsive to treatment with anti-inflammatory agents. In accordance with the present invention, the said compounds are administered to non-human animals in order to treat inflammation.

The compounds of the present invention may be administered orally, topically, parenterally, or rectally, and the invention provides a pharmaceutical composition comprising a compound of Formula I or II together with a non-toxic diluent, carrier or coating. Orally administrable compositions are preferably tablets or capsules, but pills, troches, lozenges, syrups and elixirs are also contemplated. Powders, creams, gels, ointments and lotions are suitable for topical administration and suppositories for rectal administration. Injectable compositions preferably contain a buffering agent.

The optimum dose will of course depend on the particular compound being used and the type and severity of the conditions being treated. Although the optimum quantities of the compounds of this invention to be used in such manner will depend on the activity of the particular compound, the particular type of disease condition treated, and the reaction sensitivity of the patient, oral dose levels of preferred compounds in the range of 1—100 mg/kg per day (preferably in the range of 2—50 mg/kg per day) are useful in the control of arthritic conditions. Comparative dosages may be used in topical, parenteral or rectal administration.

Compounds of the present invention have further been found to show analgesic, anti-pyretic, diuretic, anti-fibrinolytic and hypo-glycemic activity and if used for any

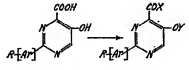
of the above activities, the same dosage ranges and conditions as discussed above for anti-inflammatory activity will apply.

In accordance with the present invention, the arylpyrazine and pyrimidine carboxylic acids of this invention are prepared by the methods set forth below.

A. *2-Aryl-5-hydroxy-4-pyrimidinecarboxylic acid*

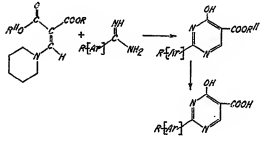
Reaction of a substituted benzamidine with glyoxal in alkaline solution followed by treatment of the formed glyoxal-amidine addition product with glyoxylic acid in basic medium results in the formation of a 2-aryl-5-hydroxy-4-pyrimidinecarboxylic acid, (Example III).

The 2-aryl-5-hydroxy-4-pyrimidinecarboxylic acids can be converted to the corresponding esters and amides by known methods. The 5-hydroxy group can also be converted to the desired derivative by known methods.



B. *2-Aryl-4-hydroxy-5-pyrimidinecarboxylic acid*

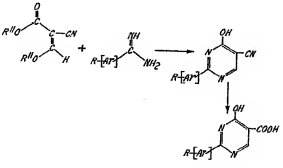
When a substituted benzamidine is reacted with a dialkyl piperidylmethylenemalonate in a metal alkoxide medium, the product obtained is an alkyl 2-aryl-4-hydroxy-5-pyrimidinecarboxylate. This is then hydrolysed in base to the corresponding carboxylic acid (Examples IV).



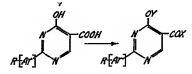
where R'' is alkyl.

A further method of preparation is the use of a dialkyl morpholinylmethylenemalonate, dialkyl ethoxymethylenemalonate or alkyl metal-α,γ-dicarboxyglutaconate in place of the dialkyl piperidylmethylenemalonate in the above synthesis.

Aromatic benzamidines when condensed with an alkyl alkoxymethylenecyanoacetate in metal alkoxide media result in 5-cyano-2-aryl-4-hydroxypyrimidines. These are then hydrolysed to the 2-aryl-4-hydroxy-5-pyrimidine-carboxylic acids by mineral acids. (Example IV).

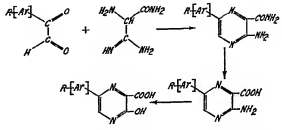


The 2-aryl-4-hydroxy-5-pyrimidinecarboxylic acids can be converted to the corresponding esters and amides by known methods. The 4-hydroxy group can also be converted to the desired derivative by known methods.

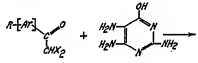


C. *5-Aryl-2-hydroxy-3-pyrazinecarboxylic acid*

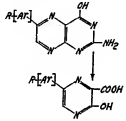
Condensation of aminomalonamidamidine with aryl glyoxals results in 5-aryl-2-amino-3-pyrazinecarboxamides. Hydrolysis of the amide in base followed by reaction of the 2-amino compound with nitrous acids in aqueous solution gives the desired 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids (Example I).



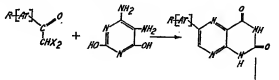
A further method of preparation involves condensation of 2,4,5-triamino-6-hydroxypyrimidine with a 2,2-dihaloacetophenone to form a 2-amino-6-aryl-4-hydroxypteridine. Upon heating in a basic medium, the desired 5-aryl-2-hydroxy-3-pyrazinecarboxylic acid is formed (Example I).



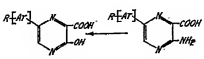
where X is halo



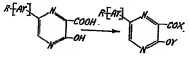
When 5,6-diaminouracil is condensed with 2,2-dihaloacetophenones in the same manner as above, the corresponding 6-aryllumazines are prepared. Heating at raised temperatures in the presence of base results in 5-aryl-2-amino-3-pyrazinecarboxylic acids which are then reacted with nitrous acid in aqueous solution to produce the 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids (Example I).



Where X is halo

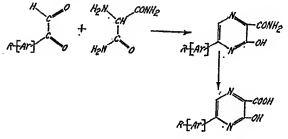


The 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids can be converted to the corresponding esters and amides by known methods. The 2-hydroxy group can also be converted to the desired derivative by known methods.

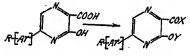


D. *6-Aryl-2-hydroxy-3-pyrazinecarboxylic acid*

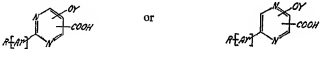
The preparation of 6-aryl-2-hydroxy-3-pyrazinecarboxylic acids involves condensation of aryl glyoxals with aminomalondiamide. 6-Aryl-2-hydroxy-3-pyrazinecarboxamides are formed, which are then hydrolysed to the corresponding 6-aryl-2-hydroxy-3-pyrazinecarboxylic acids. (Example II).



The 6-aryl-2-hydroxy-3-pyrazinecarboxylic acids can be converted to the corresponding esters and amides by known methods. The 2-hydroxy group can also be converted to the desired derivative by known methods.

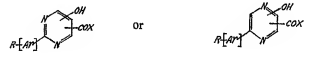


The conversion of the COOH group to a COX group is conveniently carried out by reacting a compound of the formula:



where —COX and —OY are *ortho* to each other and [Ar], R and Y are as defined above with a reactive inorganic acid halide, followed by treatment with a compound of formula HX where X is as defined above, the product then having the formula I or II above.

The phenolic OH group in a compound of formula:



in which [Ar], R and X are as defined above can be acylated by means of an alkanoic acid anhydride to produce a compound of formula I or II in which Y is alkanoyl.

The starting materials for use in the process of this invention are known.

The following are detailed examples which show the preparation of the various compounds described in this invention. They are to be construed as illustrations of said compounds and not as limitations thereof. The term 'mmole' means 'millimole'; temperatures are on the Centigrade scale.

Example I 5-Aryl-2-hydroxy-3-pyrazine carboxylic acid.

EXAMPLE I—1.

2-Amino-5-(p-fluorophenyl)-3-carboxamide

To a solution of aminomalonamidamidinc dihydrochloride (7.5 g., 0.04 mole) in ice-cold water (250 ml.) is added a solution of *p*-fluorophenylglyoxal (prepared by the procedure outlined in *C.A. 49*: 6956d; and *52*: 1095b) (7.0 g., 0.046 mole) in ice-cold water (150 ml.). The resulting solution is kept at 0—5° by means of an ice-bath, while ammonium hydroxide is added, with stirring, until the pH reaches 8—9. Additional ammonium hydroxide is added as required to maintain pH 8—9 during the next 30 minutes. The mixture is then stirred overnight at room temperature.

The precipitate of 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxamide is collected by filtration, and purified by recrystallization from ethanol.

When *p*-fluorophenylglyoxal in the preceding example is replaced by any of the aryl glyoxals of Table I below, the corresponding 2-amino-5-aryl-3-pyrazinecarboxamide of Table II below is obtained.

TABLE I.

p-bromophenylglyoxal
p-chlorophenylglyoxal
m-nitrophenylglyoxal
p-nitrophenylglyoxal
o-hydroxyphenylglyoxal
p-methylphenylglyoxal
p-methoxyphenylglyoxal
3-hydroxy-4-methoxyphenylglyoxal
3,5-dimethoxyphenylglyoxal
p-butylphenylglyoxal
2,4-dimethylphenylglyoxal
p-dimethylaminophenylglyoxal
3,4-diethoxyphenylglyoxal
2-chloro-4-methylphenylglyoxal
p-trifluoromethylphenylglyoxal
p-cyanophenylglyoxal
p-(butylthio)phenylglyoxal
p-(ethylsulfonyl)phenylglyoxal
p-phenoxyphenylglyoxal
p-benzylphenylglyoxal
p-phenethylphenylglyoxal

TABLE II.

2-amino-5-(*p*-bromophenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-chlorophenyl)-3-pyrazinecarboxamide
2-amino-5-(*m*-nitrophenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-nitrophenyl)-3-pyrazinecarboxamide
2-amino-5-(*o*-hydroxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-methylphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-methoxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(3-hydroxy-4-methoxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(3,5-dimethoxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-butylphenyl)-3-pyrazinecarboxamide
2-amino-5-(2,4-dimethylphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-dimethylaminophenyl)-3-pyrazinecarboxamide
2-amino-5-(3,4-diethoxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(2-chloro-4-methylphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-trifluoromethylphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-cyanophenyl)-3-pyrazinecarboxamide
2-amino-5-[*p*-(butylthio)phenyl]-3-pyrazinecarboxamide
2-amino-5-[*p*-(ethylsulfonyl)phenyl]-3-pyrazinecarboxamide
2-amino-5-(*p*-phenoxyphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-benzylphenyl)-3-pyrazinecarboxamide
2-amino-5-(*p*-phenethylphenyl)-3-pyrazinecarboxamide

EXAMPLE I—2.

2-Amino-5-(p-fluorophenyl)-3-pyrazinecaboxylic acid

A suspension of 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxamide (3.5 g., 0.015 mole) in 1 N sodium hydroxide (200 ml.) is heated under reflux for 8 hours. The resulting clear solution is adjusted to pH 3 with concentrated hydrochloric acid, giving 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxylic acid as a solid precipitate. The solid is collected by filtration, and recrystallized from aqueous alcohol.

When the 2-amino-5-aryl-3-pyrazinecarboxamides of Example I—1 replace 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxamide in the above example, the corresponding 2-amino-5-aryl-3-pyrazinecarboxylic acids are obtained (except in the case of 2-amino-5-(*p*-cyanophenyl)-3-pyrazinecarboxamide, from which 2-amino-5-(*p*-carboxyphenyl)-3-pyrazinecarboxylic acid is obtained).

EXAMPLE I—3.

5-(p-Fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid

A solution of 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxylic acid (560 mg., 2.4 mmoles) in cold concentrated sulfuric acid (15 ml.), is treated with a solution of sodium nitrite (250 mg., 3.6 mmoles) in cold concentrated sulfuric acid (5 ml.). The resulting solution is held at 0° for 4 hours and at room temperature for 4 hours, and then poured onto ice. The mixture is stirred overnight at room temperature and filtered. The collected solid, 5-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid, is dried and then purified by recrystallization from aqueous alcohol.

When the 2-amino-5-aryl-3-pyrazinecarboxylic acids of Example I—2 are used in place of 2-amino-5-(*p*-fluorophenyl)-3-pyrazinecarboxylic acid in the above example, the corresponding 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids of Table III below are obtained.

TABLE III

5-(*p*-bromophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-chlorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*m*-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*o*-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-methylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3-hydroxy-4-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3,5-dimethoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-butylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(2,4-dimethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-dimethylaminophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3,4-diethoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(2-chloro-4-methylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-trifluoromethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-carboxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-[*p*-(butylthio)phenyl]-2-hydroxy-3-pyrazinecarboxylic acid
5-[*p*-(ethylsulfonyl)phenyl]-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-phenoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-benzylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(*p*-phenethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid

EXAMPLE I—4.

2-Amino-6-(p-fluorophenyl)-4-hydroxypteridine

A solution of 2,4,5-triamino-6-hydroxypyrimidine dihydrochloride (4.5 g., 0.021 mole) in 50% aqueous ethanol (80 ml.) is treated with sodium acetate (13.5 g.) and 2,2-dichloro-4'-fluoroacetophenone (4.1 g., 0.020 mole). The mixture is heated under reflux for 1½ hours. 2-Amino-6-(*p*-fluorophenyl)-4-hydroxypteridine separates as a crystalline solid on cooling. It is purified by dissolution in warm 2 N sodium hydroxide, filtration, and acidification of the filtrate to pH 2.

When the following substituted 2,2-dihaloacetophenones of Table IV below are used in the above example in place of 2,2-dichloro-4'-fluoroacetophenone, the corresponding 2-amino-6-aryl-4-hydroxypteridines of Table V below are obtained.

TABLE IV.

2,2-dichloro-4'-bromoacetophenone
2,2-dichloro-2',4'-dibromoacetophenone
2,2-dichloro-pentafluoroacetophenone
2,2-2',4',5'-pentachloroacetophenone
2,2-dichloro-4'-phenylacetophenone
2,2-dichloro-4'-chloroacetophenone
2,2-dichloro-4'-methylacetophenone
2,2-dichloro-3',5'-dinitroacetophenone
2,2-dichloro-4'-methoxyacetophenone
2,2-dichloro-4'-(methylsulfonyl)acetophenone
2,2-dichloro-4'-t-butylacetophenone
2,2-dichloro-4'-hydroxyacetophenone
2,2-dichloro-2'-hydroxyacetophenone
2,2-dichloro-4'-trifluoromethylacetophenone
2,2-dichloro-4'-(methylthio)acetophenone
2,2-dichloro-2'-nitroacetophenone
2,2-dichloro-3'-nitroacetophenone
2,2-dichloro-4'-nitroacetophenone
2,2-dichloro-4'-phenethylacetophenone
2,2-3',4'-tetrachloroacetophenone
2,2-dichloro-4'-phenoxyacetophenone
2,2-dichloro-4'-benzylacetophenone

TABLE V.

2-amino-6-(4-bromophenyl)-4-hydroxypteridine
2-amino-6-(2,4-dibromophenyl)-4-hydroxypteridine
2-amino-6-(pentafluorophenyl)-4-hydroxypteridine
2-amino-6-(2,4,5-trichlorophenyl)-4-hydroxypteridine
2-amino-6-(4-biphenylyl)-4-hydroxypteridine
2-amino-6-(4-chlorophenyl)-4-hydroxypteridine
2-amino-6-(4-methylphenyl)-4-hydroxypteridine
2-amino-6-(3,5-dinitrophenyl)-4-hydroxypteridine
2-amino-6-(4-methoxyphenyl)-4-hydroxypteridine
2-amino-6-[4-(methylsulfonyl)phenyl]-4-hydroxypteridine
2-amino-6-(4-t-butylphenyl)-4-hydroxypteridine
2-amino-6-(4-hydroxyphenyl)-4-hydroxypteridine
2-amino-6-(2-hydroxyphenyl)-4-hydroxypteridine
2-amino-6-(4-trifluoromethylphenyl)-4-hydroxypteridine
2-amino-6-[4-(methylthio)phenyl]-4-hydroxypteridine
2-amino-6-(2-nitrophenyl)-4-hydroxypteridine
2-amino-6-(3-nitrophenyl)-4-hydroxypteridine
2-amino-6-(4-nitrophenyl)-4-hydroxypteridine
2-amino-6-(4-phenethylphenyl)-4-hydroxypteridine
2-amino-6-(3,4-dichlorophenyl)-4-hydroxypteridine
2-amino-6-(4-phenoxyphenyl)-4-hydroxypteridine
2-amino-6-(4-benzylphenyl)-4-hydroxypteridine

2,4,5-Triamino-6-hydroxypyrimidine may be replaced in the above example by 5,6-diaminouracil, which, with the substituted 2,2-dihaloacetophenones of Table IV above, gives the corresponding 6-aryllumazines.

EXAMPLE I—5.

5-(p-Fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid

2-Amino-6-(*p*-fluorophenyl)-4-hydroxypteridine (3.3 g., 0.013 mole) is heated in an autoclave with 4*N* sodium hydroxide (32 ml.) at 170° for 24 hours. The solution is diluted with water (32 ml.), heated to boiling, filtered, and acidified to pH 2. The precipitated 5-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid is collected by filtration and recrystallized from aqueous alcohol.

When the 2-amino-6-aryl-4-hydroxypteridines or 6-aryllumazines of Example I—4 are used in place of 2-amino-6-(*p*-fluorophenyl)-4-hydroxypteridine in the above example, the corresponding 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids or 5-aryl-2-amino-3-pyrazinecarboxylic acids, respectively, are obtained. The latter may be converted to the corresponding 5-aryl-2-hydroxy-3-pyrazinecarboxylic acids by the method of Example I—3. The products obtained are listed in Table VI below.

TABLE VI.

5-(4-bromophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(2,4-dibromophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(pentafluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(2,4,5-trichlorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-biphenylyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-chlorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-methylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3,5-dinitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-[4-(methylsulfonyl)phenyl]-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-*t*-butylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(2-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-trifluoromethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-[4-(methylthio)phenyl]-2-hydroxy-3-pyrazinecarboxylic acid
5-(2-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-phenethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(3,4-dichlorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-phenoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
5-(4-benzylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid

Example II 6-Aryl-2-hydroxy-3-pyrazinecarboxylic acid.

EXAMPLE II—1.

6-(p-Fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide

p-Fluorophenylglyoxal (5.4 g., 0.035 mole) in water (25 ml.) is treated with aqueous sodium bisulfite (d 1.34; 50 ml.), and the mixture is stirred for 45 minutes at room temperature. Aminomalondiamide (3.9 g., 0.033 mole) in water (30 ml.) is added, and the mixture is warmed for 2½ hours on the steam bath. A crystalline precipitate of 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide separates, and is collected by filtration, washed with water and ethanol, and dried. The compound is purified by recrystallization from ethanol.

When the aryl glyoxals of Example I—1 (Table I) are used in place of *p*-fluorophenylglyoxal in the preceding example, the corresponding 6-aryl-2-hydroxy-3-pyrazinecarboxamides are obtained.

EXAMPLE II—2.

6-(p-Fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid

6-(*p*-Fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide (3.7 g., 0.016 mole), sodium hydroxide (4.0 g., 0.10 mole), and ethanol (140 ml.) are heated in a steel bomb at 150° for 16 hours. After cooling, water (200 ml.) is added, and the ethanol removed by evaporation *in vacuo*. The alkaline aqueous reaction mixture is then heated to boiling, filtered hot by gravity, and the filtrate acidified to pH 4 with concentrated hydrochloric acid. The precipitate of 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid is collected after chilling, and recrystallized from alcohol.

When the 6-aryl-2-hydroxy-3-pyrazinecarboxamides of Example II—1 are used in place of 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide in the above example, the corresponding 6-aryl-2-hydroxy-3-pyrazinecarboxylic acids of Table VII below are obtained.

TABLE VII.

6-(*p*-bromophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-chlorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*m*-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*o*-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-methylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(3-hydroxy-4-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(3,5-dimethoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-butylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(2,4-dimethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-dimethylaminophenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(3,4-diethoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid

6-(2-chloro-4-methylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-trifluoromethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-carboxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-phenoxyphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-benzylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid
6-(*p*-phenethylphenyl)-2-hydroxy-3-pyrazinecarboxylic acid

Example III 2-Aryl-5-hydroxy-4-pyrimidinecarboxylic acid

2-(p-Fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid

A. A saturated (below 5°) aqueous solution of *p*-fluorobenzamidine hydrochloride (prepared by the procedure outlined in *C.A. 50*:15546) is treated with an equimolar quantity of a 40% aqueous solution of glyoxal, and the solution rendered alkaline to litmus by the addition of aqueous 50% potassium hydroxide. After 15 minutes, the crystalline addition product is collected by filtration, washed thoroughly with ice-water, and dried *in vacuo* over sulfuric acid.

B. A solution of the glyoxal-amidine addition product in ethanol (50 ml./g.) is treated with a 10—20% excess of glyoxylic acid and with aqueous 50% potassium hydroxide (5 ml./g.). The flask is tightly stoppered, and allowed to stand for several days at room temperature.

The solution is made slightly acid with acetic acid, and the precipitated 2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid collected by filtration. The product is purified by recrystallization from aqueous ethanol.

When the aromatic amidines of Table VIII below are used in place of *p*-fluorobenzamidine in the preceding example, the corresponding 2-aryl-5-hydroxy-4-pyrimidinecarboxylic acids of Table IX below are obtained.

TABLE VIII

o-chlorobenzamidine
p-chlorobenzamidine
m-nitrobenzamidine
p-nitrobenzamidine
3,4-dimethylbenzamidine
p-dimethylaminobenzamidine
p-(methylsulfonyl)benzamidine
3,5-dibromobenzamidine
2,6-dichlorobenzamidine
3,4,5-trimethoxybenzamidine
p-(butylthio)benzamidine
p-(methylthio)benzamidine
p-phenoxybenzamidine

TABLE IX.

2-(*o*-chlorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(*p*-chlorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(*m*-nitrophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(*p*-nitrophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(3,4-dimethylphenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(*p*-dimethylaminophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-[*p*-(methylsulfonyl)phenyl]-5-hydroxy-4-pyrimidinecarboxylic acid
2-(3,5-dibromophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(2,6-dichlorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-(3,4,5-trimethoxyphenyl)-5-hydroxy-4-pyrimidinecarboxylic acid
2-[*p*-(methylthio)phenyl]-5-hydroxy-4-pyrimidinecarboxylic acid
2-(*p*-phenoxyphenyl)-5-hydroxy-4-pyrimidinecarboxylic acid

Example IV 2-Aryl-4-hydroxy-5-pyrimidinecarboxylic acid

EXAMPLE IV—1.

Ethyl 2-(p-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylate

A solution of sodium (1.38 g., 0.06 g.-atom) in absolute ethanol (100 ml.) is treated with *p*-fluorobenzamidine hydrochloride (7.0 g., 0.04 mole) and diethyl piperidylmethylenemalonate [prepared by the procedure outlined by A. A. Santilli, W. F. Bruce and T. Osdene, *J. Med. Chem.*, *7*, 68 (1964)] (5.1 g., 0.02 mole). The reaction mixture is then heated under reflux with stirring for 2 hours.

The mixture is filtered, ethanol removed from the filtrate by evaporation *in vacuo*, and the residue acidified with acetic acid. The precipitated ethyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylate is collected by filtration, and purified by recrystallization from ethanol.

When the aromatic amidines of Examples III (Table VIII) are used in place of *p*-fluorobenzamidine in the above example, the corresponding 2-aryl-5-carboethoxy-4-hydroxypyrimidines are obtained.

Diethyl piperidylmethylenemalonate may be replaced in the above example by diethyl morpholinylmethylenemalonate (prepared by the procedure of A. A. Santilli, *et al.*), diethyl ethoxymethylenemalonate, or ethyl sodio-α,γ-dicarboxyglutaconate. [The latter compounds prepared by the procedure outlined by P. C. Mitten and J. C. Bardhan, *J. Chem. Soc., 123*,2179 (1923).]

EXAMPLE IV—2.

2-(p-Fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid

Ethyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylate (2.6 g., 0.01 mole) is treated with a solution of potassium hydroxide (0.7 g., 0.0125 mole) in alcohol (12.5 ml.) for 5 hours under reflux.

The solution is then evaporated to dryness *in vacuo*, and the residue taken up in water (25 ml.) The aqueous solution is filtered, the filtrate acidified with hydrochloric acid, and the precipitated 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid collected by filtration and washed thoroughly with water. The product is purified by recrystallization from alcohol.

When the 2-aryl-5-carboethoxy-4-hydroxy-pyrimidines of Example IV—1 are used in the above example in place of ethyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylate, the corresponding 2-aryl-4-hydroxy-5-pyridinecarboxylic acids of Table X below are obtained.

TABLE X.

2-(*o*-chlorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(*p*-chlorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(*m*-nitrophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(*p*-nitrophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(3,4-dimethylphenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(*p*-dimethylaminophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-[*p*-(methylsulfonyl)phenyl]-4-hydroxy-5-pyrimidinecarboxylic acid
2-(3,5-dibromophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(2,6-dichlorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-(3,4,5-trimethoxyphenyl)-4-hydroxy-5-pyrimidinecarboxylic acid
2-[*p*-(butylthio)phenyl]-4-hydroxy-5-pyrimidinecarboxylic acid
2-[*p*-(methylthio)phenyl]-4-hydroxy-5-pyrimidinecarboxylic acid
2-(*p*-phenoxyphenyl)-4-hydroxy-5-pyrimidinecarboxylic acid

EXAMPLE IV—3.

5-Cyano-2-(p-fluorophenyl)-4-hydroxypyrimidine

A solution of sodium (805 mg., 0.035 g.-atom) in absolute ethanol (100 ml.) is treated first with *p*-fluorobenzamidine hydrochloride (2.4 g., 0.014 mole), and then, after a few minutes, with ethyl ethoxymethylenecyanoacetate (2.4 g., 0.014 mole). The reaction mixture is heated under reflux with stirring for 2 hours, and then allowed to stand overnight at room temperature.

Water (50 ml.) is added, and the mixture neutralized with acetic acid. The precipitate of 5-cyano-2-(*p*-fluorophenyl)-4-hydroxypyrimidine is collected by filtration and purified by dissolution in concentrated ammonium hydroxide, followed by acidification with acetic acid.

When the aromatic amidines of Example III (Table VIII) are used in place of *p*-fluorobenzamidine in this example, the corresponding 2-aryl-5-cyano-4-hydroxypyrimidines are obtained.

EXAMPLE IV—4.

2-(p-Fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid

A mixture of 5-cyano-2-(*p*-fluorophenyl)-4-hydroxypyrimidine (2.2 g., 0.01 mole) and concentrated hydrochloric acid (10 ml.) is heated under reflux for 3 hours. It is then allowed to cool, and poured on cracked ice (*ca.* 50 g.). The precipitate is collected by filtration, and washed thoroughly with cold water.

The precipitate is treated with a slight excess of aqueous 10% sodium hydroxide, the solution filtered, and the filtrate acidified with hydrochloric acid giving 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid. The product is collected by filtration, washed with water, and recrystallized from alcohol.

When the 2-aryl-5-cyano-4-hydroxypyrimidines of Example IV—3 are used in place of 5-cyano-2-(*p*-fluorophenyl)-4-hydroxypyrimidine in the preceding example, the corresponding 2-aryl-4-hydroxy-5-pyrimidinecarboxylic acids of Table X are obtained.

Preparation of Esters.

4-Carbomethoxy-2-(p-fluorophenyl)-5-hydroxypyrimidine

To a mixture of 2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid (3.5 g., 0.015 mole) and absolute methanol (4.8 g.=6.1 ml., 0.15 mole) is added slowly, with stirring, concentrated sulfuric acid (0.6 ml.). The mixture is then heated under reflux for 8 hours.

Excess of methanol is removed by evaporation *in vacuo*, and the residue is treated, with stirring, with ice-water (25 ml.). 4-Carbomethoxy-2-(*p*-fluorophenyl)-5-hydroxypyrimidine is collected by filtration, washed thoroughly with cold water, and dried. It is purified by recrystallization from aqueous alcohol.

When the 2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid of the above procedure is replaced by any of the carboxylic acid compounds of this invention, the corresponding methyl ester is prepared.

When the methanol in the above procedure is replaced by other appropriate alcohols such as ethanol, propanol, isopropanol, butanol, isobutanol, *t*-butanol, 2-methoxyethanol or 2-ethoxyethanol, the corresponding ester is prepared. A representative list of the esters thus prepared is shown below.

Methyl 5-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylate
Methyl 5-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxylate
Methyl 5-(*p*-fluorophenyl)-2-methoxy-3-pyrazinecarboxylate
Propyl 5-(*p*-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxylate
t-Butyl 5-(*p*-trifluoromethylphenyl)-2-acetoxy-3-pyrazinecarboxylate
Methyl 5-(2-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylate
t-Butyl 6-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxylate
Methyl 6-(*o*-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylate
2-Methoxyethyl 6-(2,4-dimethylphenyl)-2-methoxy-3-pyrazinecarboxylate
Ethyl 6-[*p*-(ethylthio)phenyl]-2-hydroxy-3-pyrazinecarboxylate
Propyl 2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylate
2-Ethoxyethyl 2-(*p*-fluorophenyl)-5-acetoxy-4-pyrimidinecarboxylate
Methyl 2-(3,4,5-trimethoxyphenyl)-5-methoxy-4-pyrimidinecarboxylate
i-Propyl 2-(*p*-fluorophenyl)-4-acetoxy-5-pyrimidinecarboxylate
Methyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylate
s-Butyl 2-(2,6-dichlorophenyl)-4-methoxy-5-pyrimidinecarboxylate
Methyl 2-(*p*-dimethylaminophenyl)-4-hydroxy-5-pyrimidinecarboxylate
Methyl 2-[*p*-(methylsulfonyl)phenyl]-4-hydroxy-5-pyrimidinecarboxylate

Preparation of Alkoxy Derivatives.

2-(p-Fluorophenyl)-5-methoxy-4-pyrimidinecarboxylic acid

4-Carbomethoxy-2-(*p*-fluorophenyl)-5-hydroxy-pyrimidine (2.5 g., 0.010 mole), sodium (230 mg., 0.010 g.-atom) in anhydrous methanol (10 ml.), and methyl iodide (1.6 g., 0.011 mole) are heated together under reflux for several hours. Methanol is removed by evaporation *in vacuo*, and the residue is treated with water (25 ml.). The mixture is rendered alkaline with sodium hydroxide to ensure dissolution of unaltered starting material, and is then extracted with ether (2 × 25 ml.). The combined ethereal extracts are dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 4-carbomethoxy-2-(*p*-fluorophenyl)-5-methoxypyrimidine.

The methoxy ester is hydrolysed with alcoholic potassium hydroxide by the procedure of Example IV—2 give 2-(*p*-fluorophenyl)-5-methoxy-4-pyrimidinecarboxylic acid.

The procedure outlined in the preceding example may be applied to the preparation of other alkoxy carboxylic acids by substituting the appropriate hydroxy carboxylic acid ester for 4-carbomethoxy-2-(*p*-fluorophenyl)-5-hydroxypyrimidine and the appropriate alkyl halide for methyl iodide. A representative list of products is shown below.

2-(*p*-chlorophenyl)-5-benzyloxy-4-pyrimidinecarboxylic acid
2-(3,4-dimethylphenyl)-5-methoxy-4-pyrimidinecarboxylic acid
2-(2,6-dichlorophenyl)-5-allyloxy-4-pyrimidinecarboxylic acid
2-[*p*-(methylsulfonyl)phenyl]-5-phenethoxy-4-pyrimidinecarboxylic acid
2-[*p*-(methylthio)phenyl]-5-methoxy-4-pyrimidinecarboxylic acid
4-Ethoxy-2-(p-fluorophenyl)-5-pyrimidinecarboxylic acid

A. *Ethyl 4-chloro-2-(p-fluorophenyl)-5-pyrimidine carboxylate*

Ethyl 3-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidine carboxylate (14.3 g., 0.05 mole) is treated with phosphorus oxychloride (20 g., 0.13 mole). To the mixture, finely pulverized phosphorus pentachloride (21 g., 0.10 mole) is added in small portions. Once the evolution of hydrogen chloride has subsided, the mixture is warmed on the steam-bath for 1 hour.

Excess of phosphorus oxychloride is removed by evaporation *in vacuo*, and the residual syrup is poured onto cracked ice (ca. 50 g.). The mixture is extracted with chloroform (3 × 50 ml.), the combined extracts washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated to give ethyl 4-chloro-2-(*p*-fluorophenyl-5-pyrimidine carboxylate.

B. *Ethyl 4-ethoxy-2-(p-fluorophenyl)-5-pyrimidine carboxylate*

To a solution of sodium (2.3 g., 0.10 g. atom) in absolute ethanol (100 ml.) is added ethyl 4-chloro-2-(*p*-fluorophenyl)-5-pyrimidine carboxylate (0.015 mole). The solution is refluxed for 1.5 hours. After neutralization by passing dry CO_2 gas and centrifugation, the resultant solution is evaporated to dryness under reduced pressure. The residue is taken up in water and extracted with ether. The ethereal layer is washed with water, dried over Na_2SO_4, and evaporated. Recrystallization of the residue from aqueous acetone gives ethyl 4-ethoxy-2-(*p*-fluorophenyl)-5-pyrimidine carboxylate.

C. *4-Ethoxy-2-(p-fluorophenyl)-5-pyrimidine carboxylic acid*

The ethoxy ester is hydrolysed with alcoholic potassium hydroxide by the procedure of Example IV—2 to give 4-ethoxy-2-(*p*-fluorophenyl)-5-pyrimidine carboxylic acid.

The procedure outlined in the preceding example may be applied to the preparation of other alkoxy carboxylic acids by substituting the appropriate hydroxy carboxylic acid ester. A representative list of the products is shown below.

6-(*p*-fluorophenyl)-2-methoxy-3-pyrazinecarboxylic acid
2-(*p*-fluorophenyl)-5-methoxy-4-pynimidinecarboxylic acid
2-(*p*-fluorophenyl)-4-methoxy-5-pyrimidinecarboxylic acid
5-(*p*-chlorophenyl)-2-methoxy-3-pyrazinecarboxylic acid
5-(*m*-nitrophenyl)-2-ethoxy-3-pyrazinecarboxylic acid
5-(*p*-methylphenyl)-2-allyloxy-3-pyrazinecarboxylic acid
5-(*p*-methoxyphenyl)-2-benzyloxy-3-pyrazinecarboxylic acid
5-(*p*-trifluoromethylphenyl)-2-phenoxy-3-pyrazinecarboxylic acid
5-(3,5-dinitrophenyl)-2-methoxy-3-pyrazinecarboxylic acid
5-(4-methylsulfonylphenyl)-2-methoxy-3-pyrazinecarboxylic acid
6-(*p*-bromophenyl)-2-methoxy-3-pyrazinecarboxylic acid
6-(*m*-nitrophenyl)-2-propoxy-3-pyrazinecarboxylic acid
6-(3,5-dimethoxyphenyl)-2-vinyloxy-3-pyrazinecarboxylic acid
6-(*p*-dimethylaminophenyl)-2-benzyloxy-3-pyrazinecarboxylic acid
6-(*p*-butylthiophenyl)-2-ethoxy-3-pyrazinecarboxylic acid
2-(*o*-chlorophenyl)-4-methoxy-5-pyrimidinecarboxylic acid
2-(*p*-nitrophenyl)-4-ethoxy-5-pyrimidinecarboxylic acid
2-(*p*-fluorophenyl)-4-benzyloxy-5-pyrimidinecarboxylic acid
2-(*p*-fluorophenyl)-4-allyloxy-5-pyrimidinecarboxylic acid
2-(3,4,5-trimethoxyphenyl)-4-methoxy-5-pyrimidinecarboxylic acid

Preparation of Acyloxy Derivatives

5-Acetoxy-2-(p-fluorophenyl)-4-pyrimidinecarboxylic acid

2-(*p*-Fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid (3.5 g., 0.015 mole) is treated with acetic anhydride (3.1 g., 0.030 mole) and a catalytic amount of concentrated sulfuric acid (1 drop). The mixture is warmed on the steam-bath, with frequent agitation, for 30 minutes, and then is taken to dryness *in vacuo* to give 5-acetoxy-2-(*p*-fluorophenyl)-4-pyrimidinecarboxylic acid.

When 2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxylic acid is replaced in the above example by any of the hydroxy carboxylic acids of this invention, the corresponding acetoxy carboxylic acid is prepared. A representative list of these products is shown below.

5-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
6-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
2-(*p*-fluorophenyl)-4-acetoxy-5-pyrimidinecarboxylic acid
5-(*o*-hydroxyphenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(2,4-dimethylphenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(*p*-trifluoromethylphenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(*p*-chlorophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(pentafluorophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(2-nitrophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
5-(3-nitrophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
6-(*p*-chlorophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
6-(*p*-dimethylaminophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
6-(*p*-methoxyphenyl)-2-acetoxy-3-pyrazinecarboxylic acid
6-(*p*-butylthiophenyl)-2-acetoxy-3-pyrazinecarboxylic acid
2-(3,4-dimethylphenyl)-5-acetoxy-4-pyrimidinecarboxylic acid
2-(*p*-methylsulfonylphenyl)-5-acetoxy-4-pyrimidinecarboxylic acid
2-(*p*-chlorophenyl)-5-acetoxy-4-pyrimidinecarboxylic acid
2-(3,4,5-trimethoxyphenyl)-5-acetoxy-4-pyrimidinecarboxylic acid
2-(3,4,5-trimethoxyphenyl)-4-acetoxy-5-pyrimidinecarboxylic acid
2-(*p*-nitrophenyl)-4-acetoxy-5-pyrimidinecarboxylic acid
2-(2,6-dichlorophenyl)-4-acetoxy-5-pyrimidinecarboxylic acid
2-(*m*-nitrophenyl)-4-acetoxy-5-pyrimidinecarboxylic acid

When acetic anhydride is replaced in the above example by propionic anhydride, butyric anhydride, isobutyric anhydride, valeric anhydride, benzoic anhydride or phenylacetic anhydride, the corresponding acyloxy carboxylic acid is obtained.

Preparation of Amides

2-(p-Fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide

5-Carbomethoxy-2-(*p*-fluorophenyl)-4-hydroxy-pyrimidine (2.5 g., 0.010 mole) is refluxed for 1 hour with methanol (5 ml.) and concentrated ammonium hydroxide (15 ml.). Methanol (10 ml.) is added to the hot solution, which is then treated with charcoal, filtered, and chilled thoroughly. 2-(*p*-Fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide is collected by filtration, and recrystallized from aqueous alcohol.

When 5-carbomethoxy-2-(*p*-fluorophenyl)-4-hydroxy-pyrimidine of the above procedure is replaced by any of the esters of this invention, the corresponding carboxamide is prepared.

N,N-Diethyl 2-(p-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide

2-(*p*-Fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid (3.5 g., 0.015 mole) is added gradually to a refluxing solution of thionyl chloride (3.6 g., 0.03 mole) in benzene (15 ml.). When the addition is complete, refluxing is continued for 30 minutes.

The mixture is allowed to cool, and to it is added a solution of diethylamine (1.3 g., 0.018 mole) in benzene (15 ml.). The mixture is stirred thoroughly, warmed briefly on the steam-bath, and chilled, N,N-Diethyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide is collected, and purified by recrystallization from aqueous alcohol.

When 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxylic acid of the above procedure is replaced by any of the carboxylic acids of this invention, the corresponding N,N-diethylcarboxamide is prepared.

When the diethylamine of the above example is replaced by other appropriate primary or secondary amines such as methylamine, ethylamine, methylethylamine, benzylamine, aniline, dimethylamine, dipropylamine, cyclopropylamine, cyclohexylamine, dibenzylamine, piperidine, morpholine, piperazine, homopiperazine or pyrrolidine, the corresponding amide is prepared. A representative list of amides thus prepared is shown below.

5-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide
5-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxamide
N,N-dimethyl-5-(*p*-chlorophenyl)-2-methoxy-3-pyrazinecarboxamide
5-(2,4-dimethylphenyl)-2-hydroxy-3-pyrazinecarbopiperazide
N-ethyl-5-(*p*-methoxyphenyl)-2-hydroxy-3-pyrazinecarboxamide

6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxamide
N,N-diethyl 6-(*p*-fluorophenyl)-2-acetoxy-3-pyrazinecarboxamide
6-(*p*-nitrophenyl)-2-hydroxy-3-pyrazinecarbomorpholide
N-cyclopropyl 6-(*p*-methylphenyl)-2-ethoxy-3-pyrazinecarboxamide
N-benzyl 6-(*p*-chlorophenyl)-2-hydroxy-3-pyrazinecarboxamide
2-(*p*-fluorophenyl)-5-hydroxy-4-pyrimidinecarboxamide
2-(*o*-chlorophenyl)-5-acetoxy-4-pyrimidinecarboxamide
N,N-dimethyl 2-(*p*-dimethylaminophenyl)-5-methoxy-4-pyrimidinecarboxamide
N-phenyl 2-(*p*-nitrophenyl)-5-hydroxy-4-pyrimidinecarboxamide
2-(3,4,5-trimethoxyphenyl)-5-acetoxy-4-pyrimidinecarbopiperazide
2-(2,6-dichlorophenyl)-5-benzyloxy-4-pyrimidinecarboxamide
2-(*p*-methylthiophenyl)-5-hydroxy-4-pyrimidinecarboxamide
N-methyl 2-(*p*-fluorophenyl)-4-acetoxy-5-pyrimidinecarboxamide
N,N-dibenzyl 2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide
2-(*p*-methylsulfonylphenyl)-4-propoxy-5-pyrimidinecarboxamide
2-(3,4-dimethylphenyl)-4-phenoxy-5-pyrimidinecarbopyrrolidide
2-(*p*-fluorophenyl)-4-hydroxy-5-pyrimidinecarboxamide

Preparation of Salts

Sodio 6-(p-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylate

To a solution of 0.001 mole of sodium hydroxide in 15 ml. of water is added 0.001 mole of 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid in 10 ml. of ethanol. The mixture is stirred and heated for two hours and evaporated *in vacuo* to obtain sodio 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylate.

When one equivalent of potassium hydroxide, lithium carbonate, aluminum hydroxide, sodium carbonate or calcium hydroxide are used in place of sodium hydroxide the corresponding salt is prepared.

When the 6-(*p*-fluorophenyl)-2-hydroxy-3-pyrazinecarboxylic acid of the above procedure is replaced by any of the carboxylic acid compounds of this invention, the corresponding salt is prepared.

When two equivalents of the above bases are used in the above examples, the corresponding di- salt is prepared.

The following representative examples illustrate the interconversion or introduction of functional groups which can be accomplished at various stages of the preparation of the final products.

Methyl 6-(o-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylate

A mixture of methyl 6-(*o*-aminophenyl)-2-hydroxy-3-pyrazinecarboxylate (0.2 mole), water (600 ml.) and concentrated sulfuric acid (25 ml.) is cooled to 10°C. and a solution of sodium nitrite (0.21 mole) in a minimum of water is added gradually. When the presence of free nitrous acid is detected (starch-iodide paper), the addition is stopped and the diazotization mixture is allowed to warm to room temperature, then heated on a steam-bath until there is no more nitrogen evolution. The mixture is cooled and extracted well with chloroform, the combined chloroform layer dried and concentrated to a residue, methanol (300 ml.) is added plus 0.5 ml. concentrated sulfuric acid, the mixture is heated gently for several hours and concentrated *in vacuo* to remove most of the methanol, the residue is partitioned between chloroform and dilute sodium bicarbonate solution, and the chloroform layer dried, filtered and concentrated to a residue. Chromatography of the residue on a silica gel column using an ether-and-petroleum-ether (v/v 0—100% ether) system as eluant yields methyl 6-(*o*-hydroxyphenyl)-2-hydroxy-3-pyrazinecarboxylate.

Methyl 2-(p-methylthiophenyl)-4-hydroxy-5-pyrimidinecarboxylate

A mixture of pure methyl 5-(*p*-nitrophenyl)-2-hydroxy-3-pyrazinecarboxylate (0.01 mole) in methanol-dioxane (1:1) (ca. 200 ml.) is reacted with hydrogen at room temperature (40 p.s.i.) in the presence of 10% Pd/C (1.0 g.). The mixture is filtered, the cake washed well with methanol, the filtrate evaporated *in vacuo* and the residue chromatographed on a silica gel column using a methanol-and-methylene-chloride system (v/v 0—30% methanol) as eluant to yield methyl 5-(*p*-aminophenyl)-2-hydroxy-3-pyrazinecarboxylate.

Methyl 2-(p-methylthiophenyl)-4-hydroxy-5-pyrimidinecarboxylate

A mixture of methyl 2-(*p*-mercaptophenyl)-4-hydroxy-5-pyrimidinecarboxylate (0.01 mole) in a de-aerated aqueous KOH solution (0.01 mole) is treated with dimethylsulfate (0.012 mole) at room temperature over one hour. The mixture is acidified and extracted well with ether, and the dried ethereal extracts chromatographed on a silica gel column using an ether-and-petroleum-ether system (v/v 0—30% ether) as eluant

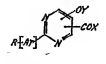
yielding methyl 2-(*p*-methylthiophenyl)-4-hydroxy-5-pyrimidinecarboxylate.

2-(p-Methylsulfinylphenyl)-5-acetoxy-4-pyrimidinecarboxylic acid

To an ice-cooled solution of 2-(*p*-methylthiophenyl)-5-acetoxy-4-pyrimidinecarboxylic acid (0.01 mole) in methanol-acetone is added a solution of sodium metaperiodate (0.01 mole) in a minimum of water, and the mixture stirred at 0—8°C. until precipitation of sodium iodate is completed. The iodate is removed by filtration, the solvents removed *in vacuo*, and the residue taken up in chloroform and ether. The combined organic extracts are dried, filtered and concentrated. Purification of the 2-(*p*-methylsulfinylphenyl)-5-acetoxy-4-pyrimidinecarboxylic acid is affected by recrystallization or chromatography (silica gel) of its methyl ester.

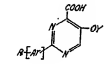
WHAT WE CLAIM IS:—

1. A compound of the formula:



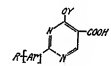
in which —COX and —OY are *ortho* to each other; [Ar] is a benzenoid or non-benzenoid aromatic structure attached to the pyrimidinyl or pyrazinyl ring either directly or through a system containing conjugated double bonds and containing one or more R radicals or atoms which may be at any position on the ring; R is a hydrogen or halogen atom or an alkyl, alkenyl, haloalkyl, hydroxy, alkoxy, acyloxy, nitro, amino, alkylamino, dialkylamino, acylmino, mercapto, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfamoyl or amino sulfinyl radical; X is a hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, N-attached N-heterocyclo, alkoxy or aralkoxy radical or a radical of formula OM, where M is an alkali metal or an equivalent of an alkaline-earth metal, magnesium or aluminium; and Y is a hydrogen atom or an alkyl, alkenyl, aralkyl, aryl, acyl or alkoxycarbonyl radical, with the proviso that Y and/or at least one R is other than hydrogen when X is hydroxy.

2. A 2-Aryl-5-hydroxy-4-pyrimidinecarboxylic acid derivative of the formula:



where [Ar], R and Y are as defined in claim 1, with the proviso that Y and/or at least one R is other than hydrogen.

3. A 2-aryl-4-hydroxy-5-pyrimidinecarboxylic acid derivative of the formula:



where [Ar], R and Y are as defined in claim 1, with the proviso that Y and/or at least one R is other than hydrogen.

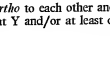
4. 2-(*p*-Fluorophenyl)-5-hydroxy-4-pyrimidine-carboxylic acid.

5. 2-(*p*-Fluorophenyl)-5-acetoxy-4-pyrimidine-carboxylic acid.

6. 2-(*p*-Fluorophenyl)-4-hydroxy-5-pyrimidine-carboxylic acid.

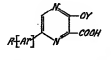
7. 2-(*p*-Fluorophenyl)-4-acetoxy-5-pyrimidine-carboxylic acid.

8. A compound of the formula:



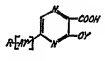
where —COX and —OY are *ortho* to each other and [Ar], R, X and Y are as defined in claim 1, with the proviso that Y and/or at least one R is other than hydrogen when X is —OH.

9. A 2-aryl-5-hydroxy-6-pyrazinecarboxylic acid derivative of the formula:



where [Ar], R and Y are as defined in claim 1, with the proviso that Y and/or at least one R is other than hydrogen.

10. A 2-aryl-6-hydroxy-5-pyrazinecarboxylic acid derivative of the formula:



where [Ar], R and Y are as defined in claim 1, with the proviso that Y and/or at least one R is other than hydrogen.

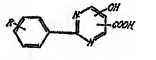
11. 2-(*p*-Fluorophenyl)-5-hydroxy-6-pyrazinecarboxylic acid.

12. 2-(*p*-Fluorophenyl)-5-acetoxy-6-pyrazinecarboxylic acid.

13. 2-(*p*-Fluorophenyl)-6-hydroxy-5-pyrazinecarboxylic acid.

14. 2-(*p*-Fluorophenyl)-6-acetoxy-5-pyrazinecarboxylic acid.

15. A compound of the formula:



in which —COOH and —OH are *ortho* to each other and R is one or more halogen substituents which may be at any position on the ring.

16. A compound as claimed in claim 15, in which R is *para*-fluoro.

17. A method of treating inflammation which comprises administering to a non-human animal a compound as claimed in any one of claims 1—14.

18. A method of treating inflammation which comprises administering to a non-human animal a compound as claimed in claim 15 or 16.

19. A pharmaceutical or veterinary composition comprising a compound as claimed in any one of claims 1—14, together with a non-toxic diluent, carrier or coating.

20. A composition as claimed in claim 19 in the form of a tablet or capsule.

21. A composition as claimed in claim 19 in the form of a pill, troche, lozenge, powder, cream, gel, ointment, suppository, lotion, syrup or elixir.

22. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 15 or 16 together with a non-toxic diluent, carrier or coating.

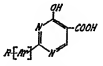
23. A composition as claimed in claim 19 or 22 that is injectable and contains a buffering agent.

24. A composition as claimed in claim 22 in the form of a pill, tablet, capsule, troche, lozenge, powder, cream, gel, ointment, suppository, lotion, syrup or elixir.

25. A process that produces a compound of the formula:

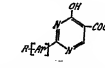
where [Ar] is a benzenoid or non-benzenoid aromatic structure attached to the pyrimidinyl ring either directly or through a system containing conjugated double bonds and containing one or more R substituents which may be at any position on the ring; R is alkyl, alkenyl, halogen, haloalkyl, hydroxy, alkoxy, acyloxy, nitro, amino, alkylamino, dialkylamino, acylamino, mercapto, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfamoyl or aminosulfinyl which comprises reacting a substituted benzamidine with glyoxal in alkaline solution, followed by treatment of the formed glyoxal-amidine addition product with glyoxylic acid under basic conditions.

26. A process that produces a compound of the formula:



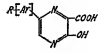
where [Ar] and R are as defined in claim 25, that comprises reacting a substituted benzamidine with a dialkylpiperidylmethylenemalonate in a metal alkoxide medium, followed by hydrolysis under basic conditions.

27. A process that produces a compound of the formula:



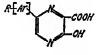
where [Ar] and R are as defined in claim 25, that comprises condensing a substituted benzamidine with an alkylalkoxymethylenecyanoacetate in a metal alkoxide medium, followed by hydrolysis with a mineral acid.

28. A process that produces a compound of the formula:



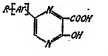
where [Ar] and R are as defined in claim 25, that comprises condensing aminomalonamidamidine with an aryl glyoxal, hydrolysing the resulting amide under basic conditions, and reacting the amine with nitrous acid in aqueous solution.

29. A process that produces a compound of the formula:



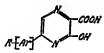
where [Ar] and R are as defined in claim 25, that comprises condensing 2,4,5-triamino-6-hydroxypyrimidine with a 2,2-dihaloacetophenone, followed by heating in a basic medium.

30. A process that produces a compound of the formula:



where [Ar] and R are as defined in claim 25, that comprises condensing 5,6-diaminouracil with a 2,2-dihaloacetophenone, heating the formed 6-aryllumazine at an elevated temperature in a basic medium, and reacting the resulting 5-aryl-2-amino-3-pyrazinecarboxylic acid with nitrous acid in aqueous solution.

31. A process that produces a compound of the formula:



where [Ar] and R are as defined in claim 25, that comprises condensing an aryl glyoxal with aminomalondiamide, followed by hydrolysis.

32. A process according to claim 25 as applied to the preparation of 2-[*p*-fluorophenyl]-5-hydroxy-4-pyrimidinecarboxylic acid.

33. A process according to claim 26 as applied to the preparation of 2-[*p*-fluorophenyl]-4-hydroxy-5-pyrimidinecarboxylic acid.

34. A process according to claim 27 as applied to the preparation of 2-[*p*-fluorophenyl]-4-hydroxy-5-pyrimidinecarboxylic acid.

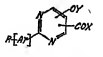
35. A process according to claim 28 as applied to the preparation of 2-[*p*-fluorophenyl]-5-hydroxy-6-pyrazinecarboxylic acid.

36. A process according to claim 29 as applied to the preparation of 2-[*p*-fluorophenyl]-5-hydroxy-6-pyrazinecarboxylic acid.

37. A process according to claim 30 as applied to the preparation of 2-[*p*-fluorophenyl]-5-hydroxy-6-pyrazinecarboxylic acid.

38. A process according to claim 31 as applied to the preparation of 2-[*p*-fluorophenyl]-6-hydroxy-5-pyrazinecarboxylic acid.

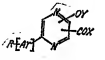
39. A process that produces a compound of the formula:



where —COX and —OY are *ortho* to each other and [Ar], R, X and Y are as defined in claim 1, that comprises reacting a compound of the formula:

where R, [Ar] and Y are as defined in claim 1, with a reactive inorganic acid halide, followed by treatment with a compound of the formula HX where X is as defined in claim 1.

40. A process that produces a compound of the formula:



where —COX and —OY are *ortho* to each other and [Ar], R, X and Y are as defined in claim 1, that comprises reacting a compound of the formula:

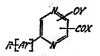
where —COX and —OY are *ortho* to each other and R, [Ar] and Y are as defined in claim 1, with a reactive inorganic acid halide, followed by treatment with a compound of the formula HX where X is as defined in claim 1.

41. A process that produces a compound of the formula:

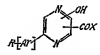
where —COX and —OY are *ortho* to each other, [Ar], R and X are as defined in claim 1 and Y is alkanoyl, that comprises reacting a compound of the formula:

where [Ar], R and X are as defined in claim 1, with an alkanoic acid anhydride.

42. A process that produces a compound of the formula:



where —COX and —OY are *ortho* to each other, [Ar], R and X are as defined in claim 1 and Y is alkanoyl, that comprises reacting a compound of the formula:



where [Ar], R and X are as defined in claim 1, with an alkanoic acid anhydride.

43. A process according to claim 41 as applied to the preparation of 2-(*p*-fluorophenyl)-5-acetoxy-4-pyrimidinecarboxylic acid.

44. A process according to claim 41 as applied to the preparation of 2-(*p*-fluorophenyl)-4-acetoxy-5-pyrimidinecarboxylic acid.

45. A process according to claim 42 as applied to the preparation of 2-(*p*-fluorophenyl)-5-acetoxy-6-pyrazinecarboxylic acid.

46. A process according to claim 42 as applied to the preparation of 2-(*p*-fluorophenyl)-6-acetoxy-5-pyrazinecarboxylic acid.

47. A process according to any one of claims 25—31 in which R is halogen.

48. A process that produces a compound as claimed in claim 1, substantially as hereinbefore described in any one of the foregoing examples.

49. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 25—48 or an obvious chemical equivalent of such a process.

50. A pharmaceutical or veterinary composition comprising a compound as claimed in claim 49 and a pharmaceutical diluent, carrier or coating.

51. A composition as claimed in claim 50 in the form of a tablet or capsule.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1972.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.